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TITLE: Improving Diagnosis of Sepsis After Burn Injury Using a Portable Sepsis Alert System

PRINCIPAL INVESTIGATOR: Ravi S. Radhakrishnan, MD, MBA, FACS, FAAP

RECIPIENT: The University of Texas Medical Branch at Galveston
              Galveston, TX 77555-5302

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6. AUTHOR(S)
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5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The University of Texas Medical Branch at Galveston
301 University Boulevard
Galveston, TX 77555-5302

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Background: Sepsis is the leading cause of death after significant burn injury. Severely burned patients (TBSA >20%) have sepsis rates < 40%. Early initiation of antibiotics within 1 hour of recognition of sepsis is the only factor associated with better survival. Diagnosis of sepsis after burn injury is not amenable to standard sepsis criteria. To address this problem, the American Burn Association developed specific criteria to prompt sepsis workup. Despite these guidelines, these findings can be subtle leading to delays in recognition of sepsis. **Hypothesis:** Best practice guidelines using 'new vital signs' of heart rate variability, regional tissue oxygenation, and noninvasive cardiac output can diagnose burn sepsis earlier, reducing morbidity and mortality. **Rationale:** Heart Rate Variability (HRV), regional Tissue Oxygenation, and non-invasive Cardiac Output (CO), have shown promise in detecting sepsis in other patient populations. These modalities have not been evaluated for sepsis detection after burn injury. **Specific Aims/Study Design:** 1. Prospectively collect traditional and 'new vital signs' and compare the diagnostic accuracy, time to diagnosis, and prediction of outcome. 2. Develop a best practice guideline for the early diagnosis and treatment of sepsis in the burn patient, integrating current and new vital signs, and incorporating these into a bedside decision-support tool. 3. Design and conduct a prospective, multicenter, randomized study to test the efficacy of the newly developed bedside tool in detecting sepsis. **Relevance:** The use of 'new vital signs' will provide an improved assessment of burn sepsis, enabling earlier detection of sepsis. The results of the study may change the standard of burn care if it is found that 'new non-invasive vital signs' can detect sepsis earlier, leading to earlier initiation of antibiotics and improved morbidity and mortality.

15. SUBJECT TERMS

Nothing listed

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	16	19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified			

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

> Despite multiple advances in critical care and resuscitation, sepsis is the leading cause of death in patients who sustain a significant burn injury. Our over-arching hypothesis is that best practice guideline using 'new vital signs' of heart rate variability, regional tissue oxygenation, and noninvasive cardiac output can be used to diagnose sepsis earlier, reducing morbidity and mortality after burn injury.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

> Burn injury, sepsis, mortality, heart rate variability, regional tissue oxygenation, noninvasive cardiac output

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals and objectives of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

> Task 1. Test the efficacy of "new noninvasive vital signs" of HRV, regional tissue oxygenation, and noninvasive cardiac output in detecting sepsis after burn injury. Proposed Timeline: Months 0-18. Patients to be enrolled: 20. Patients enrolled to date: 10. Adjusted completion date: Month 44.
> Task 2. Identify and use best conventional and "new" vital signs for early detection of burn sepsis to create a best practice guideline for identification of burn sepsis. Proposed Timeline: Months 6-18. Adjusted completion date: Month 40.
> Task 3. Create decision support tool using best practice guidelines. Proposed Timeline: Months 12-24. Adjusted completion date: Month 48.
> Task 4. Validate the efficacy of the bedside decision support tool to detect burn sepsis using multicenter, prospective study, bedside laptops, and patient sensors. Proposed Timeline: Months 48-60.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Task 1. Test the efficacy of "new noninvasive vital signs" of HRV, regional tissue oxygenation, and noninvasive cardiac output in detecting sepsis after burn injury.

During the past year, we have continued to screen patients from the Blocker Burn Unit in Galveston. Patient enrollment has had delays as outlined in the quarterly progress reports. Since completion of Y2, we have been enrolling patients (for a total of 9 quarters). In the reporting period, we have screened 37 patients and identified 2 patients who met eligibility requirements for the study. We were unable to enroll these patients in the study. One patient refused to give consent and the other patient did not have family available who could give consent and was not able to give consent himself. In order to increase patient enrollment, we changed our study entry criteria to include patients from age 13-18. Based on historic volumes of patients in the pediatric burn unit at the Shriner's Hospital For Children in Galveston, we will complete initial patient enrollment in 6-8 months (months 42-44). We have submitted IRB documents to the Shriner's Hospital IRB committee and have received initial approval, pending final review and approval by the Shriner's Hospital Main Office. We will submit then submit this documentation for HRPO approval. We will continue to work to enroll adult patients under our current IRB and HRPO protocols at UTMB.

	Screened	Eligible for Study	Enrolled in Study
# of Patients	37	2	0

Task 2. Identify and use best conventional and "new" vital signs for early detection of burn sepsis to create a best practice guideline for identification of burn sepsis.
Task 3. Create decision support tool using best practice guidelines.

Post-doctoral Fellow (Min Zhu) has analyzed publicly available data in burn patients to develop early version of predictive algorithm using HRV alone. The MIMIC II waveform dataset from Physionet is a multicenter collaboration of ICUs in the Boston area. They have collected high resolution waveform data on adult patients entering the ICU at the participating sites. The data has been deidentified and is available for all to use without IRB approval. Using this dataset, we were able to identify a total of 16 patients who sustained burn injuries (12 non-septic and 4 septic) of TBSA 20% or greater. Using the heart rate waveform data available as well as the narrative provided for each patient file, we were able to practice with signal data to identify significant heart rate variability characteristics that were different between the two groups. Based on this limited data set, we were able to identify that mean RR interval, SDNN (standard deviation of RR interval), and SD1 (the width of the perpendicular axis on Poincare plot) as significantly different metrics between septic and non-septic burn patients.

Using similar MIMIC II data from septic patients with urinary tract infections (26 non-septic and 13 septic), we performed similar analysis to begin practicing data analysis with large data sets. We identified SDN, SDNN, RMSNN, pNN50, HF, SD1, and SD1/SD2 as significantly different HRV characteristics in patients with sepsis from UTI. We attempted similar analysis with patients with pneumonia, however the results are still being interpreted.

The MIMIC II waveform data was used solely to practice data analysis techniques. While the findings are interesting, the data itself is difficult to extrapolate to practice because the dataset is limited in a few ways. Specifically, the timing of sepsis development is unclear as is the timing of the waveform in relation to time of patient's hospital course (i.e. some septic patients may have waveforms while on antibiotics while some might not). While this served as valuable experience for our team in their data analysis, it will not be used to in lieu of our prospectively obtained data from patients enrolled in the study.

Next, we acquired heart rate waveform data from historical experiments done in a swine model of traumatic brain and hemorrhagic shock by our collaborators. These experiments were conducted on an IACUC approved protocol (#1201002) as part of another study on closed loop resuscitation. Using the waveforms collected from this earlier experiment, we were able to identify SDNN, pNN50, and SD1 as significantly different in animals with hemorrhagic shock receiving TBI.

The purpose of these preliminary studies was to allow us to work with large waveform data sets to establish methodology for signal processing as well as identifying the minimum amount of data required to allow for analysis of the heart rate waveform. Based on our findings, we were able to determine that as little as 2 hours of high quality signal data were necessary to perform our signal analysis. In patient care settings, the signal obtained is rarely of consistent, high quality. Factors such as patient movement, dislodged leads, variability in lead placement, and poor connections lead to significant variability in the heart rate signal quality. In order to remove unusable segments of waveform data, signal processing methodology and software was created to take large segments of heart rate data and eliminate unusable segments. No data obtained from patients from the DoD study were used to perform this preliminary analysis.

Task 4. Validate the efficacy of the bedside decision support tool to detect burn sepsis using multicenter, prospective study, bedside laptops, and patient sensors. Proposed Timeline: Months 48-60.
UT Houston site is awaiting local IRB approval. The monitoring equipment for their site is in house and is being installed currently. Specifically, laptops to record data, the powerlab device to convert analog signals to digital, and the Osypka Cardiotronics ICON device are available. Data collection and equipment training will be completed in the next 4-6 weeks. We have made multiple trips to this site to help setup the study with Dr. Wade. Data collection will commence once IRB approval and HRPO approval is obtained. IRB approval for UT Southwestern site as well as discussion with UTSW PI for equipment installation are ongoing.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops,

conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Continue to enroll eligible patients from the Blocker Burn Unit. Continue development and improvement of predictive algorithm as new patients are enrolled. Begin patient enrollment at UT Houston. Will continue to work with PI at UTSW to begin patient enrollment. Have broadened enrollment criteria to include patients from 13-18 years old. Await final approval from Shrine Main office to begin enrollment.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge,

theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

> Nothing to report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

> Nothing to report.

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:
- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

> Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:
- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes.
Remember that significant changes in objectives and scope require prior approval of the agency.

Our initial grant proposal included age criteria of 18 years old or more. Based on slowing patient enrollment, we have expanded our entry criteria to include patients from age 13-18. We have submitted the IRB paperwork and have received preliminary approval, pending review from the main Shrine Office in Tampa, FL. Once this approval is obtained, we will submit the HRPO paperwork for approval from the DoD.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

As outlined above, patient enrollment at our institution has been slower than expected. In order to improve our ability to complete the initial patient enrollment, we have lowered our minimum age to 13 to increase the number of eligible patients available for the study.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

We were able to identify a more cost-effective methodology to obtain patient data from Cardiotronic ICON monitor, allowing us to collect both ECG waveform as well as noninvasive CO. This will allow us to shift the savings to obtain more patient sensors to enroll more patients.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Change in enrollment criteria was conditionally approved on October 17, 2017 by the IRB committee. We have made the necessary updates to the consent forms and await the final approval.

Significant changes in use or care of vertebrate animals.

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

1. Nunez Lopez O, Zhu M, Wolf J, Bohanon FJ, Kramer GC, **Radhakrishnan RS**. Heart Rate Variability Detects TBI Shortly after Injury in Swine Model of Hemorrhage. Military Health System Research Symposium, August 16, 2016. Kissimmee, FL. (poster presentation using previously performed IACUC approved experiments)

2. Nunez Lopez O, Wang X, Zhu M, Bohanon FJ, Cambiaso-Daniel J, Rontoyanni V, Finnerty CC, Lee JO, Herndon DN, **Radhakrishnan RS**. Heart Rate Variability as a Diagnostic Tool in Burn Sepsis. Joint Meeting North & South Texas Chapters of the American College of Surgeons. February 23-25, 2017. Austin, TX. (poster presentation using MIMIC II database)

3. Zhu M, Shoja MA, **Radhakrishnan RS**. Heart Rate Variability Detects Sepsis from Urinary Tract Infection during the First Two Hours after ICU Admission. The 16th International Conference on Complex Acute Illness, July 27, 2017. Milan, Italy. (poster presentation using data from MIMIC II database)

4. Zhu M, Wolf J, Bohanon FJ, Nunez-Lopez OA, Kramer GC, **Radhakrishnan RS**. Heart Rate Variability Detects Burn Injury with/without Sepsis from MIMIC II Data. Military Health System Research Symposium, August 28, 2017. Kissimmee, FL. (poster presentation using MIMIC II database)

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

  > Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

  > Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*

- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

> Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

> *Example:*
>
> *Name:*   *Mary Smith*
> *Project Role:*   *Graduate Student*
> *Researcher Identifier (e.g. ORCID ID): 1234567*
> *Nearest person month worked:*   *5*
>
> *Contribution to Project:*   *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
> *Funding Support:*   *The Ford Foundation (Complete only if the funding support is provided from other than this award).*

Name: Ravi Radhakrishnan
Project Role: PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 4
Contribution to Project: Dr. Radhakrishnan has worked to obtain IRB/HRPO amendment approval. Working with Min Zhu, he has begun to analyze patient data obtained. Have also assisted in enrolling patients in the study. Currently working on developing the multivariable predictive algorithm to identify sepsis using preliminary data. Working with collaborators in UT Houston and UTSW to begin patient enrollment at these sites. Dr. Radhakrishnan has presented preliminary work on algorithm development at MHSRS 2016 and 2017 as well as at ICCAI 2017.

Name: Min Zhu
Project Role: Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 12
Contribution to Project: Dr. Zhu continues to maintain and provide support for the data collection systems that are in place. Has built and is installing data collection system for UT Houston site. Has made multiple trips to the UT Houston site to assist in remote site preparation. Will complete training of UT Houston personnel on data collection in next 4-6 weeks. He is currently working with our collected data with Dr. Radhakrishnan to refine decision support algorithm development. Has performed data analysis and presentation preparation for talks at national and international meetings by Dr. Radhakrishnan.

Name: Omar Nunez-Lopez/Claire Cummins
Project Role: Research Associate/Fellow
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 12 total (9 for Dr. Nunez-Lopez, 3 for Dr. Cummins)
Contribution to Project: Dr. Nunez-Lopez has worked on patient enrollment, ensuring that data is collected appropriately from patients, assisting bedside nursing with adherence to data collection protocols, and ensuring that sensors are in proper position for data collection. He has assisted Dr. Zhu in setting up the remote sites to recruit patients. In addition, he has worked to maintain compliance with IRB approved protocols as well as complete necessary paperwork to change the IRB approved protocols. Dr. Nunez-Lopez returned to the UTMB Surgery Residency program to continue his residency training on 7/1/2017. Dr. Claire Cummins has entered the Radhakrishnan Lab from the UTMB Surgery Residency program to pursue 2 years of research training and has assumed Dr. Nunez-Lopez's prior role and functions.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)
- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report.

8. **SPECIAL REPORTING REQUIREMENTS**

   COLLABORATIVE AWARDS: N/A

   QUAD CHARTS: N/A

9. **APPENDICES:** N/A